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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,446	10/24/2000	Suzana Petanceska	0630/1G184-US1	2608

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,446	PETANCESKA ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,20-25 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 20-25 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed on 3-14-05 is acknowledged.

Claims included in the prosecution are 1-6, 20-25 and 31-33.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 4-6, 20-25 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the level of amyloid-beta peptides in vivo by administering 17 beta estradiol, does not reasonably provide enablement for a method of delaying or reducing the likelihood or ameliorating a disease or disorder associated with amyloidosis and which diseases include Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Instant invention is based on the apparent decrease in the levels of amyloid beta peptides using estradiol at a dose, which does not affect the soluble APP levels. First of all, as evident from the literature (Jaffe et al (JBC of record), treatment with physiological levels of estradiol in vitro results in large increases in soluble APP and according to applicant that observing no effect on this soluble APP levels is surprising after estradiol administration. However, instant claims are drawn to 'estrogen compound' and according to instant specification

on pages 8 and 9 multitudes of compounds having a steroidal structure fall within this generic term. There is no evidence in instant specification that in vivo administration of any compound falling within this generic term would lead to the same surprising results. There is no adequate guidance in the specification as to how one can determine the amounts of the compounds, which would not have an effect on the soluble APP, but decrease the levels of beta peptides. Furthermore, there is no evidence presented in the specification as to how one can predict the susceptibility of a human to Alzheimer's disease and how the treatment of these people with estrogens would delay or reduce the likelihood or ameliorating Alzheimer's disease, let alone other diseases wherein amyloidosis is involved. Broad claims must have broad basis of support in the specification; in the absence of such support, claims must be limited to estradiol effect on amyloid beta peptide levels without having an effect on the soluble APP; it would require undue experimentation to determine which of the compounds falling within the definition of 'estrogen compound' would have the same effect. In this context, it should be pointed out that the reference of Heikkinem et al (Experimental Neurology, 2004) submitted by applicant teaches that Estrogen treatment does not affect beta amyloid accumulation and plaque formation thus, showing the unpredictability in the treatment of Alzheimer's disease.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that instant specification describes in detail various estrogen compounds and methods for testing estrogen compounds and for determining effective amounts of estrogen compounds. These arguments are not found to be

persuasive since the arguments and the experiments resulting in these arguments are based on a single compound 17-beta estradiol. Applicant extrapolates the results obtained using two doses of estradiol (1 mg and 5 mg) to even treatment and prevention of numerous diseases including Alzheimer's. According to the specification, even testosterone and other steroids, which lead to the formation of various estrogens and testosterone, are included in the generic term. Mammalian bodies produce estrogens and testosterones and the amounts of the administered estradiol appear to be close to the physiological levels (on Kg basis) in humans. As already pointed out above, there is evidence in the literature regarding the unpredictability regarding estrogen treatment, beta amyloid accumulation, plaque formation and Alzheimer's disease. The rejection is maintained.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 20, 21, 23, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Washburn (5,719,137).

As pointed out above, instant claims are drawn to 'estrogen compound' with multitudes of compounds having steroidal structure included.

Washburn discloses the effectiveness of 7 alpha dihydroequilenin and compares it with estradiol in a method of reducing the risk of Alzheimer's disease and the

method of treating other dementia related conditions in males and females. The composition is administered in a transdermal patch (control release) (abstract, col. 3, lines 22-60, col. 8, lines 2-3, examples and claims). The reference meets the requirements of instant claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that The 137 patent discloses the use of 7 a-dihydroequilenin for the prevention of neurodegeneration and cognitive dysfunction associated with AD and other dementia related disorders. The 137 patent describes that, in order to test the effect of 7 a-dihydroequilenin, rats are administered 7 a-dihydroequilenin and dendrite spine densities in the brains of the rats are examined. Results indicated that 7 a-dihydroequilenin has a protective effect on hippocampal CA I region dendritic spines, an area of the brain known to be involved in cognitive functions. These arguments are not persuasive since instant claims recite "a method of delaying or reducing the likelihood of or ameliorating, a disease or disorder" and the disorder claimed is Alzheimer's disease. The prior art on col. 3, lines 26-35 clearly states, "The present invention additionally provides a method of using 17 alpha-dihydroequilenin to reduce the risk of Alzheimer's disease---". The reference meets the requirements of instant claims. The mechanism by which a compounds acts to treat or reduce the risk of getting a disease has no patentable weight when the prior art teaches the same compound and same disease.

5. Claims 1-3, 5-6, 20, 21, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al (Nature Medicine, vol. 4, April, 1998, pp. 447-451).

Xu et al disclose that estrogen (estradiol) reduces neuronal generation of Alzheimer beta-amyloid peptides, in particular A beta42 and thereby delay or prevent AD (abstract and entire article).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Washburn (5,719,137) cited above.

The teachings of Washburn have been discussed above. What is lacking in Washburn is the administration to be for at least 10 days. Since this parameter depends upon various factors such as the severity of the condition and the age of the patient, it is deemed to be an obvious parameter manipulatable by an artisan to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that 137 patent does not teach or suggest any dose of 7 alpha-dihydroequilenin that has nay effect on A beta or on the soluble APP levels. This argument is not found to be persuasive since as pointed out above, the mechanism by which a compound acts in treating a disease has no significance. Furthermore, applicant himself has not shown that Alzheimer's disease can be ameliorated with

compounds, which a mammalian body normally produces, or numerous compounds falling within that definition.

8. Claims 22, 23 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al cited above.

The teachings of Xu have been discussed above. What are lacking in Xu et al is the use of estrogens other than estradiol, the use of estrogens in a controlled release device, the amounts and the protocol of administration. It would have been obvious to one of ordinary skill in the art to use instant conjugated estrogen with a reasonable expectation of success since estrogen receptors are the same and the conjugated estrogen is used in the art in estrogen replacement therapy. The use of a controlled release device such as a transdermal patch would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success, since these are available commercially. Instant protocol of administration (for 10 days) and the amounts are deemed to be a manipulatable parameter since as pointed out above, this depends on various factors such as the severity of the condition and the age of the patient.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Xu teaches away from instant invention because in Xu, the soluble APP levels are increased. This argument is not found to be persuasive since the rejected claims are drawn to "a method of delaying or reducing the likelihood of or ameliorating, a disease or disorder" and the disorder claimed is Alzheimer's disease. Xu is clearly suggestive of delaying or preventing AD and the mechanism by which the same claimed compound taught by the prior art works has no significance.

9. Claims 1-6, 20-25 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48488 in combination with Washburn (5,510,342), Holland (3,843,662) or Lundeen (Endocrinology, vol. 138, pp. 1552, 1997) individually or taken together.

WO teaches that blood cholesterol levels correlate with the production of amyloid protein and are predictors of populations at risk of developing Alzheimer's disease (AD). According to WO, methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD (abstract, pages 1-6, Example 3 and claims). What is lacking in WO is the use of estrogens.

Washburn discloses that estrogens and conjugated estrogens lower blood cholesterol (table 1 on col. 4; col. 7, line 67 through col. 8, line 22).

Holland teaches that lowering of blood cholesterol by estrogens is known (col. 1, lines 25-28).

Lundeen similarly teaches that estrogens (estradiol and ethinyl estradiol) reduce plasma cholesterol levels (abstract, Results and Discussion).

It would have been obvious to one of ordinary skill in the art to use estrogens in the teaching of WO, that is, for lowering the levels of A beta peptide and decrease the risk of developing Alzheimer's disease since Washburn, Holland, and Lundeen teach that estrogens and conjugated estrogens lower cholesterol and because WO teaches that methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD. In the absence of showing the criticality, instant doses and protocol of administration are deemed to be obvious parameters

manipulated by an artisan since these depend upon the severity of the condition and the age of the patient.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that 488 does not teach estrogen compounds, their doses that reduce A beta levels and not affecting APP levels. These arguments are not found to be persuasive since WO clearly establishes the correlation between cholesterol levels, amyloid proteins and Alzheimer's disease and shows the effect of cholesterol lowering compounds in lowering the production of A beta thereby decreasing the risk of developing AD. Therefore, instant method would have been obvious to one of ordinary skill in the art based on the combined teachings of WO, Washburn, Holland or Lundeen. As pointed out above, applicant himself has not shown that numerous compounds falling within the generic term have the ability to treat or reduce or delay the onset of diseases such as Alzheimer's where amyloid peptides are involved. Instant specification neither shows no unexpected results in terms of treating the diseases claimed nor establishes the criticality of the soluble APP levels.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

G S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK